PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/675, 31/44, 31/60

A1

(11) International Publication Number: **WO 99/53928**

(43) International Publication Date: 28 October 1999 (28.10.99)

(21) International Application Number: PCT/CA99/00331

(22) International Filing Date: 16 April 1999 (16.04.99)

(30) Priority Data:
09/061,173 16 April 1998 (16.04.98) US

(71) Applicants: UNIVERSITY OF MANITOBA [CA/CA]; 202 Administration Building, 56 Chancellors Circle, Winnipeg, Manitoba R3T 2N2 (CA). MEDICURE INC. [CA/CA]; 24–62 Scurfield Boulevard, Winnipeg, Manitoba R3Y 1M5 (CA).

(72) Inventors: DAKASHINAMURTI, Krishnamurti; 9934 Crest View Park Drive, Winnipeg, Manitoba R2Y 0V7 (CA). SETHI, Rajat; 68 Sauve Crescent, Winnipeg, Manitoba R2N 3K9 (CA). DHALLA, Naranjan, S.; 52 Riverpoint, Winnipeg, Manitoba R2M 5N6 (CA).

(74) Agent: HIRONS, Robert, G.; Ridout & Maybee, 18th floor, 150 Metcalfe Street, Ottawa, Ontario K2P 1P1 (CA).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TREATMENT OF IATROGENIC AND AGE–RELATED HYPERTENSION AND PHARMACEUTICAL COMPOSITIONS USEFUL THEREIN

(57) Abstract

Hypertension in mammalian patients, especially elderly human patients, derived from ingestion of NSAIDs or through the normal aging process is treated by administration to the patient of a vitamin B_6 (or derivative) supplement. Where the patient requires the continued administration of an NSAID for pharmacological purposes, the NSAID is administered in conjunction with a vitamin B_6 supplement. The invention further provides combination pharmaceutical combinations of an NSAID and a vitamin B_6 supplement, e.g. orally administrable tablets or capsules, for use in treating such conditions.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TREATMENT OF IATROGENIC AND AGE-RELATED HYPERTENSION AND PHARMACEUTICAL COMPOSITIONS USEFUL THEREIN

FIELD OF THE INVENTION

This invention relates to pharmaceutical compositions and combinations, and uses thereof in medical treatment. More specifically, it relates to treatment of hypertension and to pharmaceutical compositions and combinations useful therein, especially treatment of hypertension in human patients on NSAID treatment.

BACKGROUND OF THE INVENTION

The occurrence of hypertension (elevated blood pressure) in the elderly is high. This is also the age group with a high incidence of arthritis. Osteo-arthritis is common after the age of 40. The presence of an inflammatory component to osteo-arthritis is now recognized. About 30% of patients with arthritis also have hypertension. Thus there is a considerable potential for the concurrent prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and anti-hypertensives in the elderly population group. It is estimated that, in the United States, more than 20 million people are on concurrent anti-hypertensive and NSAID therapy. It is known that most anti-hypertensive agents are less effective in the presence of NSAIDs.

In the past several years, there have been various reports of adverse effects of NSAIDs in patients receiving any form of anti-hypertensive medication such as β-blockers, angiotensin converting enzyme inhibitors and diuretics. The hypotensive (blood pressure lowering) effect of β-blockers is attenuated by the combined administration of NSAIDs such as indomethacin, sulindac and piroxicam. Significant attenuation of the hypotensive effect of the angiotensin-converting enzyme inhibitor captopril by indomethacin, acetylsalicylate and

sulindac has been reported. The antagonism by NSAIDs of the hypotensive effects of diuretics such as furosemide and hydrochlorothiazide has also been reported. Naproxen and piroxicam have been reported to raise blood pressure of patients significantly during the concomitant use of drugs such as β-blockers and diuretics. Most NSAIDs appear to reduce the anti-hypertensive effect of a variety of anti-hypertensive drugs, with the exception of the calcium channel blockers, which in any event have recently been reported to have other adverse side effects. Patients with renal impairment are at a risk of developing renal side effects when NSAIDs are used. In the elderly population suffering from various arthritic disorders, the potential adverse interaction between anti-inflammatory and anti-hypertensive drugs poses a significant problem. Treatments that maintain the anti-hypertensive action would be very beneficial to this age group.

BRIEF REFERENCE OF THE PRIOR ART

Paulose, C.S., Dakshinamurti, K., Packer, S.C. and Stephens, N.L., "Sympathetic Stimulation and Hypertension in the Pyridoxine-deficient Rat", Hypertension, Vol. 11, pages 387-391, 1988, reports work that shows that a moderate deficiency of vitamin B_6 in rats causes hypertension which is reversed within 24 hours by the administration of vitamin B_6 in the form of pyridoxine.

U.S. Patent 4,374,841 reports that pyridine derivatives such as 4,5-dihydroxymethyl-3-[2-hydroxy-3-(2-methylphenoxyethylamino)-propoxy]-2-methylpyridine and 4,5-dihydroxyethyl-3-[2-hydroxy-3-(2-methoxyphenoxyethylamino)-propoxy]-2-methyl-pyridine reduce the epinephrine-increased blood pressure in dogs.

Some nutritional studies, namely Vanderjagt, D.J. and Garry, P.J., "Vitamin B_6 Status in a Health Elderly Population", Ann. N. Y. Acad. Sci., Vol. 585, page 562-564, 1990, and Kok, F.J. et al., "Low Vitamin B_6 Status in Patients with Acute Myocardial Infarction", Am. J. Cardiol., Vol. 63. pages 513-516, 1989, indicate that the elderly may be at increased risk for developing a deficiency of vitamin B_6.

It is an object of the present invention to provide novel pharmaceutical combinations which are useful in treating hypertension in patients.

It is a further and more specific object to provide combinations of NSAIDs with other pharmaceutical, which can be used for treating hypertension without serious loss of the anti-inflammatory activity of the NSAID.

It is a further object to provide novel treatments of hypertension in patients suffering therefrom and under NSAID treatment, especially in adult human patients.

SUMMARY OF THE INVENTION

The present invention is based upon the discovery that vitamin B_6 and derivatives thereof attenuate the hypertension induced by anti-inflammatory drugs such as the NSAIDs. Blood pressure in hypertensive mammals is significantly and rapidly reduced by administration to the patient of vitamin B_6 or derivative supplement. Meta analysis of various studies indicates that the ingestion of NSAIDs attenuates the anti-hypertensive effect of a variety of anti-hypertensive drugs such as β-blockers, angiotensin-converting enzyme inhibitors and diuretics, which reduces or even negates the usefulness of such

drugs as anti-hypertensives when NSAIDs are also used.

Thus according to one aspect of the present invention, there is provided a method of alleviating hypertension in a mammalian patient who has hypertension under treatment by NSAIDs, which comprises administering to the patient an effective amount of a vitamin B_6 supplement or vitamin B_6 derivative supplement.

According to another aspect, the present invention provides a process of treating a mammalian patient in need of the beneficial effects of a non-steroidal anti-inflammatory drug (NSAID) without causing excessive hypertension in the patient, which comprises administering to the patient an effective amount of an NSAID in conjunction with a vitamin B_6 supplement or vitamin B_6 derivative supplement.

According to a further aspect, the invention provides pharmaceutical compositions for treating NSAID-induced hypertension in aged mammalian patients, comprising an effective amount of a vitamin B_6 supplement or vitamin B_6 derivative supplement.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Since elderly human patients commonly suffer from osteo and rheumatoid arthritis or similar conditions for which NSAIDs are the recommended treatment, and since elderly patients commonly suffer from hypertension, the present invention is particularly suitable for use with elderly human patients, and this is its preferred application. Thus it is of particular significance under conditions (i) where the patient is ingesting anti-inflammatory drugs, including over-the-counter anti-inflammatory drugs, e.g. for treatment of osteo or rheumatoid

arthritis, and (ii) in age-related hypertension in the elderly. However, the invention is not so limited and provides beneficial effects for substantially all mammalian patients suffering from hypertension.

The range of NSAIDs which can be beneficially included in the compositions and treatments according to the present invention is very wide, and extends to substantially all of the known NSAIDs currently available on the market. Specific NSAIDs which may be used in the present invention include diclofenac, indomethacin, the various anti-inflammatory acetylsalicylates (e.g. aspirin), sulindac, alclofenac, amfenac, piroxicam, naproxen, fenoprofen, ibuprofen, ketoprofen, flurbiprofen, alminoprofen, ketorolac, GOBAB (3-amino-4-hydroxybutyric acid), amixetrine, diflunisal, mefenamic acid, phenylbutazone, tiaprofenic acid and tolmetin. Specifically preferred are diclofenac, indomethacin and the acetylsalicylates.

The vitamin B_6 derivatives contemplated for use in the present invention are those which are chemical modifications of vitamin B_6, sometimes formed in the body as metabolites thereof, and having the same ring nucleus, for example pyridoxal-5-phosphate, pyridoxal, pyridoxamine, 4-pyridoxic acid, etc.

The vitamin B_6 supplement used in the present invention is preferably pyridoxine in any of its pharmaceutically acceptable forms, such as pyridoxine hydrochloride addition salt. The amount of vitamin B_6 compound or supplement used in the present invention is preferably from about 10 mg to about 500 mg, most preferably from about 50 to about 100 mg, per 70 kg of body weight of the patient, of vitamin B_6 pyridoxine hydrochloride, or related compound acting as a vitamin B_6 (or derivative) supplement, for administration on a daily or twice daily basis,

to an adult human patient.

The amount of NSAID administered to the patient, in the process of the invention, does not normally change from the prescribed dosage being used to treat the inflammatory condition in the absence of the vitamin B_6 (or derivative) supplement. Thus, a patient taking a daily dosage of, say, 500 mg of naproxen to treat or alleviate an underlying inflammatory condition continues to take the same prescribed 500 mg thereof supplemented by vitamin B_6 or derivative in the process of the invention. Suitable prescribed doses vary widely according to the chose of NSAID, the underlying conditions it is intended to alleviate, and factors concerning the individual patient. Generally appropriate dosage ranges may be found by consulting standard reference pharmacopeias, and thus are well within the skill of the art. As examples, indomethacin is commonly prescribed for rheumatoid arthritis at an oral dosage rate of 75-200 mg per day, in three separate doses per day. Diclofenac is commonly prescribed for rheumatoid arthritis and osteoarthritis, at a daily oral dosage rate of 75-150mg, in three separate doses per day. Acetylsalicylates are generally administered in higher dosages, such as 650 mg, four to six times per day as necessary to alleviate the symptoms. The same NSAID dosage rates as prescribed, are continued in the process and formulations of the invention.

A specific preferred embodiment of the present invention is a dosage form pharmaceutical composition for administration to patients requiring NSAID therapy, comprising in combination an effective amount of an NSAID and an amount of vitamin B_6 (or derivative) supplement effective to alleviate the hypertensive effects of the NSAID. Such a formulation suitably takes the form of an orally administrable tablet or capsule, with

appropriate inert, tablet forming ingredients. The amount of NSAID in such a tablet or capsule may be in the range of 25-1000 mg, depending on choice of NSAID, condition to be treated, frequency of administration, etc. The amount of vitamin B_6 (or derivative) supplement in such a tablet or capsule may be in the range 10-500 mg. Such a combined drug formulation provides effective therapy upon administration.

Whilst it is most convenient and preferred to prepare and use compositions which comprise a combination of the NSAID and the vitamin B_6 or derivaative, e.g. in a tablet or capsule form, along with suitable pharmaceutical carriers, diluents, excipients and the like, for oral administration, other methods of administration are within the scope of the present invention. For example, the active ingredients, namely the NSAID and vitamin B_6 or derivative, may be administered separately and sequentially to the patient, and the combined or sequential administration may be via the oral route, or alternatively parenterally, intramuscularly, rectally, transcutaneously or nasally. Formulations of the compositions of the present invention for such forms of administration are standard and within the skill of the pharmaceutical compounders art.

Vitamin B_6 is a known but not commonly prescribed anti-hypertensive agent, although not previously known to be effective in the presence of NSAIDs. A substantial advantage of its use is that it is known to be non-toxic and to lack side effects in the proposed human dosage of up to 600 mg/person/day, having previously been so used, for example, in long term treatment of chronic anemia.

SPECIFIC EXAMPLES

The following specific examples further describe and illustrate the present invention and its use, but are not to be construed as limiting on the scope of the invention. They describe the invention in relation to its use on laboratory animals, in accordance with approved practices. Laboratory rats, some having a moderate hypertension condition and some being normal, normotensive rats were used, taking measurements of their systolic blood pressure in acute and long term experiments using compositions according to the invention. The hypertensive rats were on a vitamin B_6 deficient diet for 8-10 weeks prior to the experiments. They had a body weight of 200-225 g. The control normotensive rats weighed about 300 g.

EXAMPLE 1 - (Control)

The time and dosage response of hypertensive rats to treatment with diclofenac was investigated.

Vitamin B_6 deficiency-induced hypertensive rats (prepared according to the procedures of Paulose et al., cited above) were used in acute experiments. They were injected with varying doses of diclofenac and the changes in systolic blood pressure (SBP) were monitored by tail cuff plethysmography. In vitamin B_6-deficient hypertensive rats (SBP, 150 mm Hg), intraperitoneal injection of diclofenac sodium (dose, 1 mg/kg body weight) raised the SBP by 9 mm Hg in one hour after injection. A higher dose (3 mg/kg) elevated SBP by 28 mm Hg, which also occurred one hour after injection. A larger dose (10 mg/kg) caused an increase of SBP of similar magnitude but the effect lasted for 2 hours.

EXAMPLE 2 - (Control)

The effects of treatment with indomethacin on the SBP of hypertensive rats was investigated.

The effect of varying doses (1 or 3 mg/kg body weight) of indomethacin on the SBP of hypertensive rats was examined by monitoring SBP tail cuff plethysmography following intraperitoneal injection of the drug or vehicle to the rats. Indomethacin (3 mg/kg) raised the blood pressure of hypertensive rats by 6 mm Hg within thirty minutes. The peak response (35 mm Hg) was reach by one hour. Although the effect declined by two hours, it was still elevated (15 mm Hg) and vehicle injected levels were reached only after three hours. A smaller dose (1 mg/kg) did not have any effect on the SBP of the hypertensive rat.

In the following Examples 3, 4 and 5, the effects of oral administration of various NSAIDs up to seven days on the SBP of rats on a normal diet were examined. Older (chronological age) normal rats (400-600 g body weight) on a commercial rat diet (chow) were used. These rats had a SBP of 145-150 mm Hg.

EXAMPLE 3

The effect of oral administration of a vitamin B_6 supplement (2.5 or 5 times the daily requirement) on SBP of older rats was examined. The rats were divided into four groups. Group 1 was continued on the same commercial rat chow ration. Group 2 was fed the same diet containing diclofenac (100 mg per kg diet). Group 3 was fed the commercial rat chow diet containing a vitamin B_6 supplement (2.5 or 5 times the daily requirement for vitamin B_6, i.e. 25 mg/kg and 50 mg/kg

respectively). Group 4 was fed diclofenac as in Group 2 but also had the vitamin B_6 supplement in the same amounts. The animals consume about 15 grams of chow per day. The SBPs were determined on days 0 (6 hours after start of feeding), 1 and 7, at the same time (late afternoon) for each measurement. The results are given in Tables 1(a) for 2.5 times vitamin B_6 supplement and in Table 1(b) for 5 times vitamin B_6 supplement. In the Tables, each value is the mean ± S.E.M. of 5 rats. Body weight is indicated by B.Wt., systolic blood pressure by SPB and heart rate by HR.

Table 1(a)

	0 Day on Diet			1 Day on Diet			7 Days of Diet		
Group	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)
1	413 ± 6	145 ± 1	345 ± 5	-	148 ± 2	350	418 ± 18	146 ± 1	345 ± 5
2	414 ± 15	145 ± 2	335 ± 10	-	148 ± 1	345 ± 5	418 ± 20	147 ± 1	330 ± 5
3	431 ± 7	146 ± 1	350 ± 9	-	135*± 1	345 ± 5	446 ± 9	136*± 1	325 ± 11
4	415 ± 6	145 ± 2	345 ± 5	-	123*± 2	335 ± 13	416 ± 11	120*± 2	325 ± 8

*P< 0.05 with respect to normal chow or normal chow plus Diclofenac (100 mg/kg diet)

TABLE 1(b)

	0 Day on Diet			1 Day on Diet		
Group	B.Wt. (g)	SBP (mm Hg)	HR (beat/ min)	B.Wt. (g)	SBP (mm Hg)	HR (beat/ min)
1	565 ± 15	148 ± 1	345 ± 10	-	147 ± 1	350 ± 10
2	560 ± 13	148 ± 1	350 ± 12	-	149 ± 1	350 ± 10
3	563 ± 16	148 ± 1	350 ± 8	-	124*± 1	350 ± 10
4	561 ± 12	149 ± 1	330 ± 8	-	108*± 1	335 ± 8

*P<0.05 with respect to normal chow or normal chow plus Diclofenac (100 mg/kg diet)

These results indicate that, even on day 1, vitamin B_6 supplementation alone gives a significant decrease in SBP (Group 3 results in comparison with Group 1 results). Diclofenac alone had little effect (Group 2 results), but the combination of vitamin B_6 supplement and diclofenac (Group 4) was most marked. Vitamin B_6 supplement decreased the SBP of older rats. The effect was quite significant even when the rats were receiving diclofenac. The higher dose of vitamin B_6 resulted in a larger effect. The effect of vitamin B_6 supplementation was seen as early as one day after the treatment and was still seen one week after initiation of the supplementation regimen.

EXAMPLE 4

The experiments reported in Example 3 were essentially repeated using a different et of essentially the same animals, but substituting indomethacin at the same amounts, for diclofenac. Each experiment used 1.5 times vitamin B_6 supplement. The results are given in Table 2, corresponding to the previous Tables.

TABLE 2

	0 Day on Diet			1 Day on Diet			7 Days of Diet		
Group	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)
1	437 ± 8	149 ± 2	320 ± 12	-	150 ± 2	320 ± 15	467 ± 8	149 ± 1	325 ± 11
2	480 ± 24	150 ± 1	320 ± 12	-	150 ± 1	340 ± 19	411*± 10	150 ± 2	331 ± 12
3	480 ± 17	148 ± 2	325 ± 11	-	134*± 1	335 ± 6	521 ± 16	132*± 5	355 ± 15
4	452 ± 7	148 ± 1	340 ± 10	-	124*± 2	350 ± 18	408 ± 2	116*± 1	344 ± 6

*P<0.05 with respect to normal chow or normal chow plus Indomethacin (100 mg/kg diet)

These results are comparable to those reported in Table 1(a).

Vitamin B_6 supplementation decreased the SBP of rats. This was quite significant in rats getting indomethacin, in addition.

EXAMPLE 5

In these experiments, the effects of the vitamin B_6 supplement 2.5 times the daily requirement) on the SBP of the older rats on commercial rat ration but receiving acetyl salicylate (20 or 100 mg per kg. diet) in the diet were investigated. The experiments were conducted as described in Example 1. Different sets of essentially the same animals were used. Table 3(a) reports the results with animals of four groups.

Group 1 was fed normal chow.
Group 2 was fed normal chow.
Group 3 was fed chow with 2.5 x vitamin B_6.
Group 4 was fed chow with 2.5 x vitamin B_6 plus acetylsalicylate (20 mg/kg diet).
Each Value is the Mean ± S.E.M. of 5 rats.

TABLE 3(a)

	0 Day on Diet			1 Day on Diet			7 Days of Diet		
Group	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)
1	443 ± 13	150 ± 1	330 ± 9	-	150 ± 2	330 ± 12	450 ± 10	150 ± 2	325 ± 10
2	450 ± 11	150 ± 2	325 ± 11	-	150 ± 3	300 ± 12	416*± 14	149 ± 1	315 ± 6
3	443 ± 21	148 ± 1	330 ± 9	-	137*± 1	335 ± 10	456 ± 16	132*± 1	300 ± 8
4	453 ± 13	149 ± 2	345 ± 5	-	124*± 1	355 ± 15	367 ± 8	116*± 1	340 ± 10

*P< 0.05 with respect to normal chow or normal chow plus acetylsalicylate

Table 3(b) reports similarly the results of experiments in which the Group 2 and Group 4 animals received 100 mg/kg acetylsalicylate instead of 20 mg/kg - otherwise the experiments were the same.

Table 3(b)

	0 Day on Diet			1 Day on Diet			7 Days of Diet		
Group	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)
1	560 ± 10	149 ± 1	345 ± 10	-	149 ± 1	340 ± 10	-	149 ± 1	350 ± 10
2	558 ± 15	148 ± 2	350 ± 10	-	148 ± 1	350 ± 15	-	148 ± 1	350 ± 10
3	565 ± 10	148 ± 1	345 ± 10	-	136*± 1	345 ± 10	-	133*± 1	350 ± 11
4	555 ± 12	148 ± 1	350 ± 10	-	125*± 1	340 ± 10	-	123*± 1	350 ± 12

*P< 0.05 with respect to normal chow or normal chow plus acetylsalicylate.

As in the previous experiments, vitamin B_6 supplementation decreased the SBP of these rates. The effects were most significant in rats receiving the anti-inflammatory

drug.

EXAMPLE 6

The effect of diclofenac administration with and without co-administration of vitamin B_6 was studied in young hypertensive rats as described in Example 3, but using a daily dosage of diclofenac of 10 mg/kg and continuing the treatment for 60 days. As before, four groups of rats were used, each group comprising 6 animals. Group 1 received a normal commercial chow ration daily. Group 2 received the same chow ration daily, supplemented with the diclofenac. Group 3 received the same chow ration daily, supplemented with 25 mg/kg vitamin B_6. Group 4 received the same chow ration daily, supplemented with both diclofenac and vitamin B_6 at the aforesaid amounts. The results are given below in Table 4.

TABLE 4

Group	Day 0		Day 60	
	Body wt (g)	SBP	Body wt	SBP
1	255±12	121±2	502±10	151±3
2	272±14	125±1	512±12	169±2
3	267±14	131±2	497±16	123±2
4	258±13	127±1	676±13	138±1

n=6, $P<0.05$ compared to Group 1 and Group 2, $P<0.05$ compared to Groups 1, 3 and 4.

The results reported in connection with these Examples lead to the conclusion that moderate vitamin B_6 deficiency causes a modest hypertension in mammals. The administration (i.p.) of non-steroidal anti-inflammatory drugs exacerbates the hypertension in acute experiments. Administration of vitamin B_6 or a derivative thereof attenuates the hypertensive potential of the NSAIDs. In longer term experiments the oral administration of a vitamin B_6 (or derivative) supplement to older mammals results in a significant decrease in the SBP of these mammals which were still receiving NSAIDs. The co-administration of vitamin B_6 (or derivatives) and NSAIDs results in a significant decrease in the SBP of older mammals.

WE CLAIM:

1. A method of alleviating hypertension in a mammalian patient who has hypertension under treatment by NSAIDs, which comprises administering to the patient an effective amount of a vitamin B_6 (or derivative) supplement.

2. The method of claim 1 wherein the amount of vitamin B_6 supplement is from about 10 mg to about 500 mg per 70 kg of body weight of the patient.

3. The method of claim 2 wherein the vitamin B_6 supplement is pyridoxine hydrochloride, pyridoxal pyridoxal-5-phosphate or related compound acting as a vitamin B_6 supplement.

4. A process of treating a mammalian patent in need of the beneficial pharmacological effects of a non-steroidal anti-inflammatory drug (NSAID) without causing excessive hypertension in the patient, which comprises administering to the patient an effective amount of an NSAID and an effective amount of a vitamin B_6 supplement.

5. The process of claim 4 wherein the NSAID is administered together with the vitamin B_6 supplement.

6. The process of claim 4 wherein the NSAID is administered separately from the vitamin B_6 supplement.

7. The process of claim 4 wherein the NSAID is selected from among diclofenac, indomethacin, acetylsalicylates, sulindac, alclofenac, amfenac, piroxicam, naproxen, fenoprofen, ibuprofen, ketoprofen, flurbiprofen, alminoprofen, ketorolac, GOBAB, amixetrine, diflunisal, mefenamic acid, phenylbutazone, tiaprofenic acid and tolmetin.

8. The process of claim 7, wherein the vitamin B_6 supplement is administered in an amount of from about 10 mg - 500 mg per 70 kg body weight of the patient.

9. The method of claim 8 wherein the NSAID is diclofenac, indomethacin or an acetylsalicylate.

10. The process of claim 8, wherein the administration of the NSAID and the vitamin B_6 supplement is accomplished simultaneously, by oral administration of a capsule or tablet incorporating both the NSAID and the vitamin B_6 supplement.

11. A pharmaceutical composition useful in treating inflammatory conditions in a mammalian patient without causing development of excessive hypertension in the patient, comprising in combination an effective amount of a non-steroidal anti-inflammatory drug (NSAID) and an effective amount of a vitamin B_6 (or derivative) supplement.

12. The pharmaceutical composition of claim 11 in orally administrable form.

13. The pharmaceutical composition of claim 11 wherein the vitamin B_6 supplement is pyridoxine hydrochloride, pyridoxal, pyridoxal-5-phosphate or related compound acting as a vitamin B_6 supplement.

14. The pharmaceutical composition of claim 13 wherein the vitamin B_6 supplement is present in an amount of from about 10-500 mg.

15. The pharmaceutical composition of claim 14 wherein the NSAID is present in an amount of from about 25-1000 mg.

16. The pharmaceutical composition of claim 15 wherein the NSAID is

selected from among diclofenac, indomethacin, acetylsalicylates, sulindac, alclofenac, amfenac, piroxicam, naproxen, fenoprofen, ibuprofen, ketoprofen, flurbiprofen, alminoprofen, ketorolac, GOBAB, amixetrine, diflunisal, mefenamic acid, phenylbutazone, tiaprofenic acid and tolmetin.

17. The pharmaceutical composition of claim 16 wherein the NSAID is selected from the group consisting of diclofenac, indomethacin and an acetylsalicylate.

18. The pharmaceutical composition of claim 17 wherein the NSAID is diclofenac.

19. The pharmaceutical composition of claim 17 wherein the NSAID is indomethacin.

20. The pharmaceutical composition of claim 17 wherein the NSAID is an acetylsalicylate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00331

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/675 A61K31/44 A61K31/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 564 614 A (PFIZER) 14 January 1986 (1986-01-14) column 2, line 20-40; claim 1 column 3	4,5,7-20
X	FR 2 641 189 A (TIMOL MAMOOJEE) 6 July 1990 (1990-07-06) page 4; claims	4,5, 7-17,20
X	FR 4 492 M (CAZAUX AV) the whole document	4,5, 7-17,20
X	FR 6 723 M (C. BLUM) 17 February 1969 (1969-02-17) the whole document	4,5, 7-17,20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 September 1999	17/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kanbier, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00331

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BAKER ET AL: "Chlorthalidone-Induced Pseudoporphyria: Clinical and Microscopic Findings of a Case" JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, vol. 21, 1 November 1989 (1989-11-01), pages 1026-1029, XP002114632 page 1027, left-hand column, paragraph 1 ---	1-3
X	JACOBS: "The Neuroleptic Malignant Syndrome: Often an Unrecognized Geriatric Problem" JOURNAL OF THE AMERICAN GERIATRICS SOCIETY, vol. 44, 1 April 1996 (1996-04-01), pages 474-475, XP002114633 page 474, left-hand column, paragraph 4 ---	1-3
A	US 4 542 026 A (RIOS JOSE) 17 September 1985 (1985-09-17) column 1, line 12-14; claim 1 column 1, line 62-67 ---	1,4,11
A	DATABASE WPI Week 7848 Derwent Publications Ltd., London, GB; AN 78-86713a XP002114634 & JP 53 121765 A (CHUGAI PHARM CO LTD), 24 October 1978 (1978-10-24) abstract ---	1-3
A	FR 6 707 M (LABORATOIRES ALLARD) 17 February 1969 (1969-02-17) page 1, right-hand column, paragraph 2; claim 2 ---	1-3
A	FR 2 034 539 A (SOC D'ETUDES PROD CHIMIQUES) 11 December 1970 (1970-12-11) page 1, line 17-23; claim 3 ---	1-3
A	FR 7 503 M (SOCIÉTÉ FRANÇAISE DES LABORATOIRES LABAZ) 8 December 1969 (1969-12-08) page 2, left-hand column, paragraphs 3-5; claim 1 -----	1-3

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/00331

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-20
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

nformation on patent family members

International Application No
PCT/CA 99/00331

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4564614 A	14-01-1986	AT 64096 T	15-06-1991
		AU 558648 B	05-02-1987
		AU 4848685 A	08-05-1986
		CA 1249521 A	31-01-1989
		CN 1007959 B	16-05-1990
		CN 1038759 A	17-01-1990
		DK 463485 A	12-04-1986
		EG 17706 A	30-08-1990
		EP 0178122 A	16-04-1986
		FI 853947 A	12-04-1986
		GR 852456 A	11-02-1986
		IE 58741 B	03-11-1993
		NZ 213755 A	29-11-1988
		PH 21572 A	11-12-1987
		PH 23066 A	27-03-1989
		PH 23057 A	27-03-1989
		PH 23054 A	27-03-1989
		PT 81278 A,B	01-11-1985
		DD 238920 A	10-09-1986
		JP 1744804 C	25-03-1993
		JP 4028245 B	13-05-1992
		JP 61091124 A	09-05-1986
		US 4812455 A	14-03-1989
		US 4874757 A	17-10-1989
		US 4579846 A	01-04-1986
		US 4766117 A	23-08-1988
FR 2641189 A	06-07-1990	WO 9119500 A	26-12-1991
FR 4492 M		NONE	
FR 6723 M	17-02-1969	NONE	
US 4542026 A	17-09-1985	NONE	
JP 53121765 A	24-10-1978	NONE	
FR 6707 M	17-02-1969	NONE	
FR 2034539 A	11-12-1970	AT 297024 B	15-02-1972
		BE 745047 A	01-07-1970
		CA 933522 A	11-09-1973
		CH 503051 A	15-02-1971
		DE 2006432 A	03-12-1970
		FR 2154505 A	11-05-1973
		GB 1236531 A	23-06-1971
		NL 7001348 A,B	14-08-1970
		OA 3416 A	15-12-1970
FR 7503 M	08-12-1969	NONE	